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Haemostasis
Managing Editor: H.C. Hemker, Maastricht

Reprint
Publisher: S. Karger AG, Basel
Printed in Switzerland

Haemostasis *13:* 201–208 (1983)

0301–0147/83/0133–0201$2.75/0

Half-Life Time and Control Frequency of Vitamin K-Dependent Coagulation Factors

Theoretical Considerations on the Place of Factor VII in the Control of Oral Anticoagulation Therapy

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Key Words. Half-life times of coagulation factors · Factor VII · Control frequency of anticoagulation · Theoretical model

Abstract. A short review about the place of coagulation factor VII in the initial phase of blood coagulation is given. A theoretical model describing the relationship between the half-life times of vitamin K-dependent coagulation factors and the control frequency of oral anticoagulation therapy is presented. The constraints that control frequency imposes on the type of determination to be carried out are discussed.

Introduction

It is well known from the literature that part of the coagulation cascade reactions proceed at lipid/water interfaces. The enzymes and substrates in these surface-mediated reactions are the vitamin K-dependent coagulation factors. It is possible to regulate the efficiency of the heterogeneous catalysis through manipulation of the affinity for lipid/water interfaces of the coagulation factors involved. Oral anticoagulation is based on this principle. Today, oral anticoagulation therapy is usually controlled by a general analytical method sensitive to the overall effect on several of the vitamin K-dependent coagulation factors (VII, IX, X and II). The advent of automatable amidolytic tests measuring the different vitamin K-dependent factors independently actualizes the discussion on the relative importance of single vitamin K-dependent factors in the control of oral anticoagulation therapy. This discussion in the older literature mostly goes in the form of debates on the importance of 'factor X sensitivity' of thromboplastins. The hard facts on which one can decide what factors are important in this respect are: (1) The biological half-life times of the vitamin K-dependent coagulation factors. (2) The levels of the vitamin K-dependent coagulation factors that are acceptable to ensure adequate anticoagulation (upper limit) and to prevent bleeding (lower limit).

Whereas point 1 is well known [*van der Meer* et al., 1968], no hard data are available on point 2; it is not known, for example, whether 2.5% of factor VII will cause a serious bleeding tendency or not. In other words it is not easily predicted how a factor VII level as low as 2.5% will be expressed in the overall coagulation capacity of blood, or whether a level of 30% of factor IX will carry a significant risk of thrombosis.

Although the discussion on what level of which individual factor is acceptable has not been carried to a conclusion, in practice the decision for all practical purposes has already been made on the moment that the frequency of the control of oral anticoagulant therapy has been decided, because there is a relationship between the control frequency and the half-life time of the coagulation factors actually followed in an overall test. Qualitatively this will be easily understood. It is no use to control factor II levels daily if the response of the factor II level to changes in dosage of oral anticoagulants is limited by the fact that its biological half-life time is 2½ days. On the other hand it does not seem useful either to choose a parameter with a biological half-life of a few hours when the control frequency is only one control per 6 weeks. The situation is akin to the registration of electric phenomena on a strip-chart recorder. If the dampening of the instrument is too high, fast signals will be missed, if it is too low, too much noise will be recorded. We present in this article a theoretical model meant to explore the relation between the half-life times of the factors to be measured and the control frequency. We also discuss the constraints that control frequency imposes on the type of determination to be carried out.

Special Position of Factor VII among the Vitamin K-Dependent Coagulation Factors

Recent research in the coagulation field has shown that the familiar picture of an intrinsic and extrinsic pathway of coagulation joining at the factor X activation step is far too simple. There exist close connections between the initiating reactions of both pathways [see also the contribution of *Prydz* in this issue].

In the 'classical' concept factor VII is activated upon interaction with tissue thromboplastin and the intrinsic pathway is triggered by the exposure of blood to negatively charged surfaces. Several authors have shown that factor XII_a and Hageman factor fragments activate bovine factor VII [*Altman and Hemker,* 1967; *Kisiel* et al., 1977; *Radcliffe* et al., 1977]. *Seligsohn* et al. [1978, 1979a, b] showed in a human system that both XII_a and IX_a activate factor VII. These authors state that after surface contact, XII_a is the principal activator of factor VII and after clotting, IX_a is the principal factor VII activator. Kallikrein acts indirectly by activating factors XII and XI. *Morrison-Silverberg and Jesty* [1981] using a bovine system argued that a ternary complex of tissue factor, factor VII and factor X_a would be the form of factor VII responsible for a further generation of factor IX_a and factor X_a during the period preceding clot formation. Only 0.2% of the total plasmatic content of factor X needs to be activated to give a maximal expression of VII activity and the generation of activity in the system could be extremely rapid because it would only depend upon the formation of a Michaelis-type complex and not upon a proteolytic splitting. *Radcliffe and Nemerson* [1975, 1976] have shown that in a

purified system first there is a rapid activation followed by a slower inactivation of factor VII by factor X_a. In whole plasma, where inhibitors of factor X_a are also present, an inactivation of factor VII_a by factor X_a is not so easily proven, but it is not unlikely that also here factor X_a might exert a negative control function. Furthermore, thrombin and plasmin can also enhance factor VII activity [*Zur and Nemerson,* 1980; *Østerud* et al., 1980].

On the other hand, both in human and bovine systems factors IX and X can be activated by the tissue factor-VII_a complex [*Josso and Prou-Wartelle,* 1965; *Østerud and Rapaport,* 1977, 1980; *Jesty and Silverberg,* 1979]. It has been shown that factors IX and X are competitive inhibitors with regard to their respective activation by the tissue factor-VII_a complex. When the activation of factors IX and X was studied in a system mimicking bovine plasmatic conditions [*Jesty and Silverberg,* 1979] X activation proceeded about 7 times faster than IX activation. Using human reagents, *Østerud and Rapaport* [1980] reported that the two activation rates were equal.

Finally there are clinical indications pointing to the close connection between intrinsic and extrinsic pathways. Usually, patients with very low levels of factor XII or factor XI do not show a bleeding tendency while the hemorrhagic problems in factor VIII- and factor IX-deficient patients are well known. *Aiyappa* [1981a, b] described a chromogenic analogue of the APTT test that turned out to be sensitive not only to deficiency of the factors XII, prekallikrein, XI, IX, VIII, V, X and II but to factor VII deficiency as well. *Bertina* et al. [1981] described a patient with an abnormal factor X molecule; it is normally activated by the factors IX_a, IX_a+VIII and RVV-X but only very slowly by the thromboplastin factor VII complex. This patient never showed bleeding complications.

The short review given above [see also the article of *Prydz* in this issue] clearly shows that the extrinsic and intrinsic pathways of the coagulation cascade are intimately linked. Many experiments will be needed to completely elucidate this complicated system. However, one thing emerges very clearly: factor VII must play a central and important role in the initial phase of blood coagulation. This idea is further supported by the fact that contrary to the other vitamin K-dependent coagulation factor zymogens, factor VII has relatively strong esterase activity in its native (one-chain) form [*Zaugg,* 1980; *Zur and Nemerson,* 1980; *Radcliffe and Nemerson,* 1975]. Finally the in vitro occurrence of cold-promoted activation, the fact that factor VII_a in plasma stored at 4 °C is stable for several days [*Seligsohn* et al., 1978a, b], the persistence of activated factor VII in circulation for several hours ($t_{1/2}$ = 144 min) after transfusion of factor IX concentrates [*Seligsohn* et al., 1979a, b] and the observation that antithrombin III does not inactivate factor VII_a [*Østerud* et al., 1976; *Jesty,* 1978] all point to the special place factor VII takes among the serine esterase enzymes of the coagulation cascade.

Factor VII might be an important factor in the control of bleeding and thrombotic tendencies. Clinical assays of factor VII and its activity state in plasma could be of great diagnostic importance [*Hemker* et al., 1976; *Poller* et al., 1981; *Avvisati* et al., 1980; *Seligsohn* et al., 1978b; *Aiyappa,* 1981a, b]. On the basis of these observations the importance of measuring factor VII theoretically may be sustained. On the other hand, having in mind

the relatively short half-time value of factor VII [*van der Meer* et al., 1968] one may ask if a factor VII assay is suitable for the control of oral anticoagulation therapy when the control frequency in practice varies between once per day and once per 6 weeks.

Theoretical Model

In the following a theoretical model is presented which gives a relation between the biological half-life times of vitamin K-dependent coagulation factors and the control frequency of anticoagulation therapy. In the construction of the model it is assumed that the coagulation factor levels approach the level eventually dictated by the rate of synthesis in the liver by first-order kinetics and that the processes leading to increase respectively decrease of these levels are characterized by the same kinetic parameters [*van der Meer* et al., 1968]. Figure 1 shows a practical situation. At a given time t = 0, the level of a given vitamin K-dependent coagulation factor is α and t units of time, later the level of the same factor is β. It is not likely that during the time lapse t the coagulation factor level follows the straight line α–β; it will sometimes lie above and sometimes beneath this line. The lowest value that can be reached between two controls α and β is found when the level decreases after point α and then again increases to reach level β. This situation is represented by the line $\alpha - n_{min} - \beta$ in figure 2.

The curves α–n_{min} and n_{min}–β can be described by first-order kinetics (see above):

$$n_{min} = \alpha\, e^{-kt_{min}} \qquad (1)$$

$$\text{and } 100 - \beta = (100 - n_{min})\, e^{-k(t-t_{min})} \qquad (2)$$

Substitution of equation 1 in equation 2 gives:

$$\frac{100-\beta}{100-n_{min}} \cdot \frac{n_{min}}{\alpha} = e^{-kt}$$

which, because of the first-order character, can be rewritten as:

$$\frac{100-\beta}{100-n_{min}} \cdot \frac{n_{min}}{\alpha} = (\tfrac{1}{2})^{t/t_{\frac{1}{2}}} \qquad (3)$$

For reasons of simplicity of the calculations to follow a new variable q is introduced:

$$1/q = (\tfrac{1}{2})^{t/t_{\frac{1}{2}}},$$

rearrangement of equation 3 then gives:

$$n_{min} = \frac{100}{q\left(\frac{100-\beta}{\alpha}\right)+1} \qquad (4)$$

Equation 4 is used to calculate table I starting from the situation of stable anticoagulation ($\alpha = \beta$).

From table I it follows that when a vitamin K-dependent coagulation factor level of 20% is maintained in 'stable anticoagulation', dangerously low values (< 5%) can be reached within 3 half-time values if sudden overdosage causes blocking of the coagulation factor synthesis.

Exactly the same reasoning can be followed to find the value n_{max} between the points α and β (cf. fig. 2); for the curve α–n_{max} we can write:

$$100 - n_{max} = (100 - \alpha)\, e^{-kt_{max}} \qquad (5)$$

and for the descending limb of the curve

$$\beta = n_{max}\, e^{-k(t-t_{max})} \qquad (6)$$

Combination of equations 5 and 6 gives

$$\frac{100-n_{max}}{\alpha} \cdot \frac{\beta}{n_{max}} = e^{-kt}$$

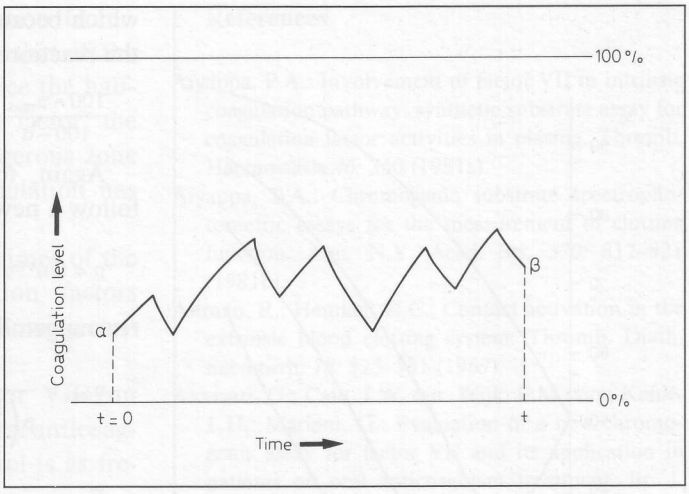

Fig. 1. Time course of the coagulation factor level between two successive controls. At the time t = 0 a level α is measured; t units of time later the level is β.

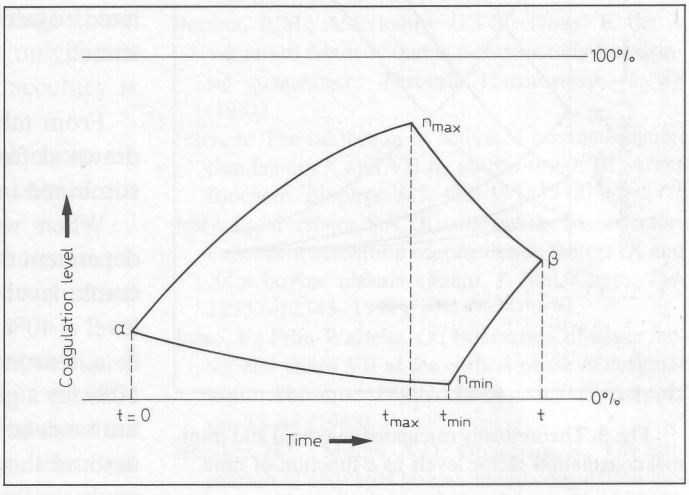

Fig. 2. Representation of the theoretically calculated maximal (n_{max}) and minimal (n_{min}) values the coagulation factor level can reach between two successive controls (α and β).

Table I. n_{min} values as a function of α, β and ($t/t_{½}$)

$t/t_{½}$:	¼	⅓	½	1	2	3	4	5
q:	1.19	1.26	1.41	2	4	8	16	32
α = β = 5	4.2	4.0	3.6	2.6	1.3	0.6	0.3	0.2
α = β = 10	8.5	8.1	7.3	5.3	2.7	1.4	0.7	0.3
α = β = 15	12.9	12.3	11.1	8.1	4.2	2.2	1.1	0.5
α = β = 20	17.4	16.5	15.1	11.1	5.9	3.0	1.5	0.8
α = β = 25	21.9	20.9	19.1	14.3	7.7	4.0	2.0	1.0
α = β = 50	45.7	44.2	41.5	33.3	20.0	11.1	5.9	3.0

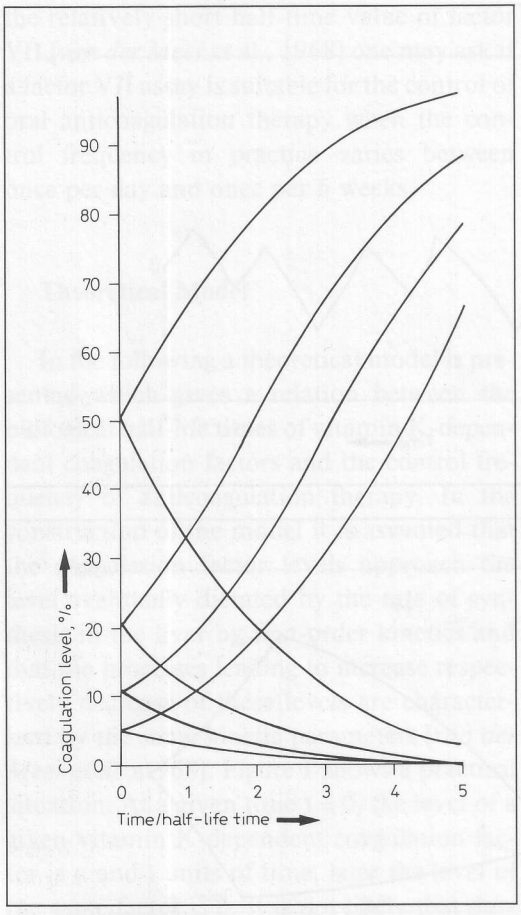

Fig. 3. Theoretically calculated maximal and minimal coagulation factor levels as a function of time.

which because of the first-order character of the reactions can be written as:

$$\frac{100 - n_{max}}{100 - \alpha} \cdot \frac{\beta}{n_{max}} = (1/2)^{t/t_{1/2}} \qquad (7)$$

Again, to simplify the calculations that follow a new variable p is introduced:

$$p = (1/2)^{t/t_{1/2}},$$

rearrangement of equation 7 then gives

$$n_{max} = \frac{100}{p\left(\frac{100 - \alpha}{\beta}\right) + 1} \qquad (8)$$

From equation 8 table II can be calculated, again 'stable' anticoagulation is assumed.

From table II similar conclusions can be drawn as from table I. Tables I and II can be combined into figure 3.

When we assume that for vitamin K-dependent coagulation factors the lowest tolerable level is 4% and the highest tolerable level is 40%, it can be seen from figure 3 that at a reasonable coagulation factor level of 10% for a given coagulation factor the lower limit can be reached within 1.5 half-time values and the upper limit within 2.6 half-time

Table II. n_{max} values as a function of α, β and $(t/t_{1/2})$

$t/t_{1/2}$:	1/4	1/3	1/2	1	2	3	4	5
p:	0.84	0.79	0.71	0.50	0.25	0.12	0.06	0.03
$\alpha = \beta = 5$	5.9	6.2	6.9	9.5	17.4	30.4	46.7	63.7
$\alpha = \beta = 10$	11.7	12.3	13.5	18.2	30.8	48.1	64.9	78.7
$\alpha = \beta = 15$	17.4	18.3	19.9	26.1	41.4	59.5	74.6	85.5
$\alpha = \beta = 20$	22.9	24.0	26.0	33.3	50.0	67.6	80.6	89.3
$\alpha = \beta = 25$	28.4	29.7	31.9	40.0	57.1	73.5	84.7	91.7
$\alpha = \beta = 50$	54.3	55.9	58.5	66.7	80.0	89.3	94.3	97.1

values of the respective coagulation factor. These calculations clearly show that if the control interval is more than twice the half-life time of a given coagulation factor, the patient may have been in a dangerous zone even if perfectly stable anticoagulation has been observed ($\alpha = \beta$).

Having in mind the half-life times of the vitamin K-dependent coagulation factors [*van der Meer* et al., 1968] the following conclusions are justified:

(1) The time course of factor VII can never be used for the control of oral anticoagulation therapy even if the control is as frequent as once per 24 h.

(2) In all cases where the control frequency is once weekly or less, the only factor that can be followed with some accuracy is factor II.

(3) Factor IX is the factor of choice in crucial situations when control is carried out daily.

(4) Factor X is the factor of choice in situations when the control has to be carried out 2–3 times weekly.

Of course the theoretical lines α–n_{min}–β and α–n_{max}–β in figure 2 represent extreme situations and in most practical situations the coagulation factor levels during the time lapse t will lie within the theoretical envelope α–n_{min}–β–n_{max} scattered around the line α–β. At the moment statistical experiments are carried out to test the theoretical model introduced above. These statistical experiments will provide knowledge about the scattering of the coagulation factor levels around the line α–β during the time lapse t. In other words, the statistical experiments will give us a realistic picture of the fluctuations in coagulation factor level during the periods between successive controls of anticoagulation therapy.

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